Commissioner of Patents
USSN 10/661,097

AMENDMENTS TO THE DRAWINGS

Please replace sheets containing figures 1a-c, 3a, 8d-i, 12a-c, 14a, 17h, 33, 35a-c and 37a-b with replacement sheets submitted herewith.

Attachment: Replacement sheets.

REMARKS

Claims 1-38 are pending in the application. Claims 1, 2 and 14, 15, 17, 18, 21, 22 and 27-29 are under examination. Claims 3-13, 16, 19, 20, 23-26 and 30-38 have been cancelled.

New claims

New claims 39-42 have been added to specifically protect various specific sequences and commercial embodiments. Support can be found on pages Example 1, 2, 3 and Figs. 1-5, 7, 8, 11-18 and 37. No new matters have been introduced. These claims should not raise any new grounds for rejection nor require a new search. It is respectfully requested that these claims be accepted and entered.

Sequence compliance

As requested by the Examiner, the specification and the drawings have been amended to provide SEQ ID NOs for the oligonucleotide sequences disclosed throughout the specification.

Election/Restrictions

Claims 3-13, and 33-38 have been cancelled, as requested by the Examiner.

Claim rejections - 35 U.S.C. § 112

Rejections of claims 1, 2 and 14-32 under 35 U.S.C. 112, first paragraph, for containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention, is maintained. The Examiner argues that the specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising oligonucleotides with non-sequence complementary modes of action and comprising random sequences, whereby prevention and treatment of HSV-1, HSV-2, or CMV's infection are obtained in an organism. The Examiner further argues that the disclosure of three effective oligonucleotides found to reduce or prevent viral infectivity of some strains of virus, and the disclosure of various

means to assay oligonucleotide candidates for effectiveness in reducing viral growth or infectivity, does not provide an adequate description of the very large genus claimed. Thus, the Declaration filed October 5, 2006 describing two oligonucleotides (REP 2006 and 2031) found to prevent HSV-2 transmission in a mouse model, as well as three oligonucleotides (REP 2006, 2031 and 2107), found to reduce CMV liver titers upon intraperitoneal administration, was not enough in order to disclose a sufficient number of oligonucleotides to represent the very broad genus claimed.

To overcome this rejection, the Applicants wish to submit that claim 1 has been amended to further define that the oligonucleotides claimed comprise at least one phosphorothioated linkage and are at least 30 nucleotides in length. Thus, former claim 19 has been cancelled in this regard to avoid redundancy. Consequently, the distinguishing features or common attributes concisely shared by the members of the genus claimed in the present application is that the oligonucleotides have at least 30 nucleotides in length and at least one phosphorothioated linkage and an antiviral activity occurring by a non-sequence complementary mode of action. Applicants wish to further submit that the antiviral activity of the claimed oligonucleotide is due to the presence of at least one phosphorothioated linkage. The oligonucleotides claimed do not have any other common feature other than being at least 30 nucleotides in length (as exemplified in the application with REP 2005, REP 2006, REP 2007, REP 2008, SEQ ID NO: 6, SEQ ID NO: 9, REP 2024, SEQ ID NO: 20, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 26, REP 2060, SEQ ID NO: 22 and SEQ ID NO: 24) and having at least one phosphorothioated linkage. Furthermore, the oligonucleotides used in the present invention and claimed in claims 1, 2 and 14, 15, 17, 18, 21, 22 and 27-29 can be randomer oligonucleotides. As defined on page 14 of the present description, the term "randomer" is intended to mean a single stranded DNA having a wobble (N) at every position, such as NNNNNNNNNN. Each base is synthesized as a wobble such that the randomer oligonucleotides of the present invention actually consist of a population of different randomly generated sequences of the same size. By the nature of the preparation used to produce them, sequence complementary mode of action cannot occur. For example, in a 15 μmol preparation of a randomer oligonucleotide containing 31 nucleotides in length, this preparation will have at most 2 copies of every possible sequence of nucleotides. Thus, the presence of 2 copies of a specific sequence cannot account for the response observed in the

present invention. Consequently, the antiviral activity of the oligonucleotides claimed in the present application and demonstrated for at least 14 different oligonucleotides *in vitro* (see Example 1, 2, 3 and Figs. 1-5, 7, 8, 11-18 and 37) and *in vivo* (see Declaration filed October 5, 2006), is not due to a sequence specificity and complementary mode of action. Thus, Applicants are entitled to claim an oligonucleotide (without reference to a specific sequence) having at least one phosphorothioated linkage and an antiviral activity occurring principally by a non-sequence complementary mode of action.

The Applicants further point out that in the present application, as acknowledged by the Examiner, results are disclosed demonstrating the antiviral activity of the oligonucleotides claimed in the present application against HSV-1, HSV-2 and CMV. More specifically, results demonstrating the antiviral activity of at least 14 different oligonucleotides of at least 30 nucleotides in length (for example REP 2005, 2006, 2007, 2018, 2018, 2021, 2024, 2029, 2030, 2031, 2055, 2056, 2057 and 2060) against HSV-1, HSV-2 or CMV *in vitro* are disclosed in Example 1, 2, 3 and Figs. 1-5, 7, 8, 11-18 and 37. Furthermore, as submitted in a Declaration filed October 5, 2006, results demonstrating the *in vivo* efficacy of two oligonucleotides (REP 2006 and 2031) to prevent HSV-2 transmission in a mouse model, as well as three oligonucleotides (REP 2006, 2031 and 2107), to reduce CMV liver titers upon intraperitoneal administration have been disclosed. Thus, the antiviral activity of the oligonucleotides claimed in the present application has been demonstrated for 14 different oligonucleotides which is believed to be a "representative number of species". Consequently, it is believed that the present application teaches a sufficient and/or representative number of varieties of species to reflect the complete genus. In view of the foregoing, reconsideration and withdrawal of the Examiner's rejection of claims 1, 2 and 14-32 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejection of claims 1, 2, and 14-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is still maintained. The Examiner argues that the specification teaches the *in vivo* inhibition of HSV-2 using oligonucleotides disclosed in the present application. These experiments are not representative of providing *in vivo* treatment or prophylaxis in order to adequately represent the genus of sequences comprising oligonucleotides of at least 29 nucleotides in length with anti viral activity, principally acting

by a non-sequence complementary mode of action. The Examiner agrees that *in vivo* efficacy has been shown for the particularly described oligonucleotides, REP 2006, 2031 and 2107, regarding the ability to prevent or reduce HSV-2 or CMV infection in an appropriate animal model, as filed in the Declaration submitted October 5, 2006. The Examiner therefore concludes that the application appears to be enabled for the ability to treat CMV upon systemic administration of REP 2006, 2031 and 2107 and for the ability to treat or prevent HSV-2 injection upon administration of REP 2006 and 2031. However, the ability of these oligonucleotides to treat or prevent HSV-2 and CMV is not correlative or representative of the ability to predict the efficacy of any randomers of 29 bases or more to provide such effects in a subject.

In order to overcome this rejection, Applicants wish to submit that claim 1 has been amended to further define that the oligonucleotides claimed comprise at least one phosphorothioated linkage and are at least 30 nucleotides in length. Further, the Applicants respectfully submit that it is clearly stated in the Manual of Patent Examining Procedure that:

> As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility.
>
> Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).
>
> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. (Manual of Patent Examining Procedure 2107.03).

It is thus believed that not only the Applicants have provided *in vitro* results demonstrating the antiviral activity of at least 14 different oligonucleotides of at least 30

nucleotides in length, but the results were correlated by the *in vivo* results demonstrating the efficacy of two oligonucleotides (REP 2006 and 2031) to prevent HSV-2 transmission in a mouse model, as well as three oligonucleotides (REP 2006, 2031 and 2107), to reduce CMV liver titers upon intraperitoneal administration have been disclosed. Consequently, Applicants believe that a reasonable correlation between the activity in question and the asserted utility has been demonstrated in the present application. Regarding the Examiner's argument that the ability of the oligonucleotides tested *in vivo* to treat or prevent HSV-2 and CMV is not correlative or representative of the ability to predict the efficacy of any randomers of 30 bases, as now claimed, or more to provide such effects in a subject, the Applicants respectfully disagree. A person skilled in the art would acknowledge that extensive data, reflecting a sufficient and/or representative number of varieties of species to reflect the complete genus, were disclosed in order to demonstrate the antiviral activity of the oligonucleotide of the present invention *in vitro*. Further, three oligonucleotides have been used to demonstrate the ability to predict the efficacy of any randomers of 30 bases or more in animal models. Thus, the *in vitro* results were predictive of the efficacy of the oligonucleotides in animal models.

In addition, regarding the Examiner's comment related to the ability of these oligonucleotides to treat or prevent HSV-2 and CMV, which in her opinion is not correlative or representative of the ability to predict the efficacy of any randomers of 30 bases or more to provide such effects in a subject, Applicants believe that the present description is enabling for the subject matter claimed in the present application. However, it is believed that in order to convince the Examiner of the enablement of the present invention, under her requirement, clinical trials would have been initiated before this application would have been filed. Requesting clinical trial results to demonstrate enablement of the present invention is unreasonable and represents an undue burden, burden that does not exist in any other field of invention. Applicants respectfully submit that it is stated in the Manual of Patent Examining Procedure (MPEP 2107.03, section IV) that:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional

law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders.

The Applicants wish to submit that, only when the pre-clinical data is promising, a company makes a decision on whether to begin the long and costly process of clinical trials. Most companies file for and receive patents for the commercial uses of the compound that they are developing during pre-clinical trials to not only protect their invention, but also to reassure investors that the invention which will be undergoing clinical phase trials is patented. Assuming the company decides to pursue human studies, it must first submit an Investigational New Drug (IND) application to the FDA for approval. The IND must provide pre-clinical data of sufficient quality to justify the testing of the drug in humans. It is believed that in order for the present invention to be commercially and financially liable, Applicants need to file a patent application before submitting an IND application to the FDA. Applicants believe that the Examiner is not examining the present application in terms of its patentability, but in terms of its liability to pursue human studies, which is believed to be the role of the FDA and not of the USPTO. Consequently, Applicants feel that, in view of the arguments presented by the Examiner, it is easier to obtain an FDA approval to start clinical phase trials than meeting the criteria of patentability imposed by the Examiner. Furthermore, it is believed that the Examiner is requesting further testing in animal models of a larger number of oligonucleotides in order to demonstrate the ability of 30 bases or more oligonucleotides to treat or prevent HSV-1, HSV-2 and CMV infection.

The Applicants also respectfully submit that the HSV-2 mouse model and the CMV mouse model used to demonstrate the ability of the oligonucleotides tested *in vivo* to treat or prevent HSV-2 and CMV are well accepted *in vivo* models for the study of pathogenesis and antiviral compound activity, as demonstrated in the references of Krmpotic *et al.* (2003, Microbes and Infection, 5: 1263-1277), Scott *et al.* (J General Virology, 86: 2141-2151), Bernstein *et al.* (2003, Antimicrobial Agents and Chemotherapy, 47: 3784-3788) and Bourne *et al.* (1999, J Infectious Diseases, 180: 203-205). In view of the foregoing, reconsideration and withdrawal of the Examiner's rejection of claims 1, 2 and 14-32 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

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No additional fees are believed to be necessitated by this amendment. Should this be in error, authorization is hereby given to charge Deposit Account No. 19-5113 for any underpayment or to credit any overpayment.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully,

Date: May 18, 2007

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Enc. Replacement sheets for drawings
Extension of time
References of Krmpotic *et al.*, Scott *et al.*, Bernstein *et al.* and Bourne *et al.*